

Date of Approval: NOV 25 2002

## **FREEDOM OF INFORMATION SUMMARY**

**NADA 137-687**

**FORMALIN-F™**

**(formalin: approximately 37% by weight of formaldehyde gas)**

“...for the use of formalin to be expanded, as a parasiticide, to all finfish and penaeid shrimp, and, as a fungicide, to the eggs of all finfish”

## **SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION**

Sponsored by:

Natchez Animal Supply Company

**NADA 137-687**

**F015-1**

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**I. GENERAL INFORMATION**

NADA Number: 137-687

Sponsor: Natchez Animal Supply Company  
201 John R. Junkin Drive  
Natchez, Mississippi 39120

Generic Name: Formalin, approximately 37% by weight of formaldehyde gas

Trade Name: FORMALIN-F™

Marketing Status: Over-the-counter

Effect of Supplement: Provides for the use of FORMALIN-F™ to be expanded, as a parasiticide, to all finfish and penaeid shrimp, and, as a fungicide, to the eggs of all finfish.

**II. INDICATIONS FOR USE**

FORMALIN-F™ is added to the environmental water as follows: (a) for the control of external protozoa (*Chilodonella* spp., *Costia* spp., *Epistylis* spp., *Ichthyophthirius* spp., *Scyphidia* spp. and *Trichodina* spp.) and the monogenetic trematode parasites (*Cleidodiscus* spp., *Dactylogyrus* spp., and *Gyrodactylus* spp.) on all finfish, (b) for the control of fungi of the family Saprolegniaceae on all finfish eggs, and (c) for the control of protozoan parasites (*Bodo* spp., *Epistylis* spp., and *Zoothamnium* spp.) on penaeid shrimp.

**III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE**

- A. Dosage Form: Formalin is a solution of approximately 37% formaldehyde gas (by weight) in water. This is equivalent to 37 grams of formaldehyde in 100 ml of solution.
- B. Route of Administration: In the environmental water
- C. Recommended Concentrations: as shown in Tables 3.1 to 3.3.

## 1. For the Control of External Parasites on Finfish

**TABLE 3.1** Concentrations of Formalin

Aquatic Species	Administer in Tanks and Raceways for up to 1 hour (μL/L)*	Administer in Earthen Ponds Indefinitely (μL/L)*
Salmon & trout		
above 50° F	up to 170	15-25**, ***
below 50° F	up to 250	15-25**, ***
All other finfish	up to 250	15-25**, ***

\* Microliter per liter (μL/L) = parts per million (ppm).

\*\* Use the lower concentration when ponds, tanks, or raceways are heavily loaded with phytoplankton, or finfish, to avoid oxygen depletion due to the biological oxygen demand created by decay of dead phytoplankton. Alternately, a higher concentration might be used if dissolved oxygen is strictly monitored.

\*\*\* Although the indicated concentrations are considered safe for cold and warm water finfish, a small number of each lot or pond to be treated should always be used to check for any unusual sensitivity to formalin before proceeding.

## 2. For the Control of Fungi of the Family Saprolegniaceae on Finfish Eggs

**TABLE 3.2** Concentrations of Formalin

Aquatic Species	Administer in Hatchery Systems (μL/L)*
Eggs of all finfish except Acipenseriformes	1000 to 2000 for 15 minutes**
Eggs of Acipenseriformes	Up to 1500 for 15 minutes**

\* Microliter per liter (μL/L) = parts per million (ppm)

\*\* Apply in constant flow water supply of incubating facilities. A preliminary bioassay should be conducted on a small sub sample of finfish eggs to determine sensitivity before treating an entire group. This is necessary for all species because egg sensitivity can vary with species or strain and the unique conditions at each facility.

## 3. For Control of External Protozoan Parasites on Penaeid Shrimp

**Table 3.3** Concentrations of Formalin

Aquatic Species	Administer in Tanks and Raceways for up to 4 hours (μL/L)*	Administer in Earthen Ponds Indefinitely (μL/L)*
Shrimp	50 to 100**	25***

\* Microliter per liter, μL/L) = parts per million (ppm).

\*\* Treat for up to 4 hours daily. Treatment may be repeated daily until parasite control is achieved. Use the lower concentration when tanks or raceways are heavily loaded with phytoplankton, or shrimp, to avoid oxygen depletion due to the biological oxygen demand created by decay of dead phytoplankton. Alternatively, a higher concentration might be used if dissolved oxygen is strictly monitored.

\*\*\* Treatment may be repeated in 5 to 10 days, if needed.

#### IV. EFFECTIVENESS

##### A. Striped Bass and all other Finfish

Formalin is a water treatment where the primary effect results from localized action at the topical site of administration. The concentration of active drug at the topical site is a function of the administered concentration and water conditions. These latter two conditions and the pathogen's drug sensitivity are considered the primary determinants of effectiveness. Although the drug may be slightly absorbed, systemic absorption is not believed to play a significant role in the drug's effectiveness at the topical site. Thus, drug concentration and the effects of the pathogen are considered to be the primary determinants of effectiveness, while differences in drug/host response among species are considered to be an insignificant factor.

FORMALIN-F™ is currently approved for its effectiveness against external protozoa (*Chilodonella* spp., *Costia* spp., *Epistylis* spp., *Ichthyophthirius* spp., *Scyphidia* spp., and *Trichodina* spp.) and monogenetic trematode parasites (*Cleidodiscus* spp., *Dactylogyrus* spp., and *Gyrodactylus* spp.), in a wide range of cold and warm freshwater finfish (see 21 CFR 529.1030). Since, as discussed above, formalin's effectiveness is based on drug concentration and the drug effects on potentially pathogenic external protozoans rather than the *in vivo* drug/host response in various species, the effectiveness of formalin against these pathogens would be the same in all species of finfish.

Therefore, the effectiveness data summarized in the attached Public Master File (PMF) 3543 and PMF 5228 are adequate to support formalin's effectiveness against the same ectoparasites on striped bass and on all other finfish.

##### B. Eggs of All Finfish

FORMALIN-F™ is currently approved for its effectiveness against fungi of the family Saprolegniaceae on salmon, trout, and esocid eggs (see 21 CFR 529.1030). Since, as discussed above, formalin's effectiveness is based on drug concentration and the drug effects on eggs rather than the individual drug/host response in various species, the effectiveness of formalin against the fungi would be the same in all species of eggs. Therefore, the effectiveness data in PMF 3543 and data existing in the publicly disclosable investigational new animal drug (INAD) file 8886 are adequate to support formalin's effectiveness against the same fungi on all finfish eggs. Studies within INAD 8886 address the safety of formalin when used on the eggs of several finfish species representing five families, including: walleye, common carp, channel catfish, white sucker, and lake sturgeon. These same studies indirectly address the effectiveness of the treatment as measured by egg hatchability, because the presence of significant fungi on finfish eggs can severely reduce hatchability.

Additional effectiveness studies are not required because it is determined that interspecies extrapolation is appropriate to demonstrate the effectiveness of formalin on the eggs of all finfish for the control of the same family of fungi (Saprolegniaceae) for which the drug is currently approved.

C. Penaeid Shrimp

Effectiveness data from the Freedom of Information (FOI) summary for PMF 3543, 6 FR 20618, May 6, 1991, demonstrated that formalin, when used as directed, is effective in the treatment and control of external protozoan parasites on shrimp.

## V. ANIMAL SAFETY

### A. Finfish

The data summarized in the FOI summary for PMF 3543 addressed the safety of formalin in salmon, trout, catfish, largemouth bass, bluegill (the originally approved set of species), as well as smallmouth bass, black bullhead and green sunfish. The results of additional studies (contained in PMF 5228) demonstrating the safety of short-term and indefinite use of formalin in striped bass, a species known to be sensitive to formalin, are described below. The data in these studies show that use of the drug at the recommended concentration is safe in a wide range of cold and warm water finfish, including striped bass, the most sensitive species. Since, as discussed above, formalin safety has been demonstrated in a wide variety of species (nine species from four of the most important North American families of cultured finfish: Ictaluridae, Salmonidae, Centrarchidae and Percichthyidae), one species (striped bass) of which has been documented as an extremely sensitive species, the safety of formalin would be the same for all finfish species. Therefore, these studies are adequate to demonstrate that use of the drug at recommended concentrations is safe in all finfish.

As noted in the Freedom of Information summary for PMF 3543, tolerances to formalin may vary with strains and species of finfish. Health status may also affect formalin tolerance. Although the indicated concentrations are considered safe for cold and warm water finfish, a small number of each lot or pond to be treated should always be used to check for any unusual sensitivity to formalin before proceeding.

In addition, formalin may be harmful to biofilters, and care should be taken to avoid contamination of the biofilter with treatment solution.

#### 1. Target Animal Safety Study #1

##### a. Name and Address of Investigator:

Wilmer A. Rogers, Ph.D.  
Department of Fisheries and Allied Aquaculture  
Auburn University, Alabama 36849

##### b. General Design of the Investigation:

- i. Purpose of the study: To determine if formalin is safe when administered to healthy striped bass.
- ii. Test Animals: Striped bass (*Morone saxatilis*) fingerlings averaging 46.7 mm in length and 0.9 g in body weight were used for this set of studies. One study was conducted at 18°C, while the other was conducted at 25°C. Sixteen aquaria (eight aerated and eight not aerated), with 20 fingerlings in each, were used in the study.

- iii. Dosage Form: Formalin solution
- iv. Route of Administration: In the environmental water
- v. Dosages Used: Untreated control, 250, 500, and 750 ppm formalin, respectively (1X, 2X, and 3X the maximum proposed concentration)
- vi. Test Duration: 3 hours
- vii. Parameters: Mortality at 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 hours of treatment
- viii. Results: Refer to Tables 5.1 and 5.2 below. No mortality occurred in fish exposed to 250 ppm formalin for up to 1.5 hour.

**TABLE 5.1** Safety of Formalin in Striped Bass at 25°C

Formalin Concentration (ppm)	Mortalities (%), with/without Aeration					
	0.5 hr	1.0 hr	1.5 hr	2.0 hr	2.5 hr	3.0 hr
0	0/0	0/0	0/0	0/0	0/0	0/0
250	0/0	0/0	0/0	50/25	50/30	65/45
500	0/0	0/0	20/45	70/90	80/100	80/100
750	10/5	75/50	100/80	100/100	100/100	100/100

**TABLE 5.2** Safety of Formalin in Striped Bass at 18°C

Formalin Concentration (ppm)	Mortalities (%), with/without Aeration					
	0.5 hr	1.0 hr	1.5 hr	2.0 hr	2.5 hr	3.0 hr
0	0/0	0/0	0/0	0/0	0/0	0/0
250	0/0	0/0	0/0	0/15	5/25	15/35
500	0/0	0/0	25/40	55/65	80/85	100/100
750	0/5	35/10	80/70	95/100	100/100	100/100

## 2. Target Animal Safety Study #2

### a. Name and Address of Investigator:

Wilmer A. Rogers, Ph.D.  
 Department of Fisheries and Allied Aquaculture  
 Auburn University, Alabama 36849



## b. General Design of the Investigation:

- i. Purpose of the study: To determine if formalin is safe when administered to healthy striped bass.
- ii. Test Animals: Striped bass fingerlings averaging 46.5 mm in length and 0.9 g in body weight were used for this study. Twenty fish were allotted to each of six treatment groups. The study was conducted at 22°C.
- iii. Dosage Form: Formalin solution
- iv. Route of Administration: In the environmental water
- v. Dosages Used: Untreated control, 55.0, 57.5, 60.0, 62.5, and 65.0 ppm formalin. Formalin was administered in flow-through aquaria with aeration.
- vi. Test Duration: 96 hours
- vii. Parameters: Cumulative mortality at 24, 48, 72, and 96 hours of treatment
- viii. Results: The 96-hour LC50 was 60.0 ppm. Refer to Table 5.3 below for mortality patterns.

**TABLE 5.3** Safety of Formalin in Striped Bass at 22°C

Formalin Concentration (ppm)	Cumulative Mortalities (%) at Different Times after Formalin Application			
	24 hr	48 hr	72 hr	96 hr
0	0	0	0	0
55.0	0	0	0	0
57.5	5	40	40	40
60.0	20	45	55	55
62.5	15	35	55	60
65.0	5	70	90	90

## 3. Target Animal Safety Study #3

Bills, T.D., L.L. Marking, and G.E. Howe. 1993. Sensitivity of juvenile striped bass to chemicals used in aquaculture. United States Department of the Interior, Fish and Wildlife Service, *Resource Publication 192*.

These studies determined LC50's (concentrations producing 50% mortality in a population) of formalin in striped bass. Ten juvenile (1.0 g) striped bass were exposed to each test concentration of formalin in 15 L glass jars. Tests were conducted at a water temperature of 12°C and at varying levels of water hardness. Observations on mortality were made at 1, 3, and 6 hours during the first day of exposure, and then once daily for 4 days. Tests were duplicated in different year class fish in waters of different temperature (12, 17, and 22°C), hardness, and pH. Mean LC50's in soft water of pH 7.5 at 12°C were as shown in Table 5.4.

**TABLE 5.4** Mean 50% Lethal Concentrations (LC50's) of Formalin to Striped Bass

Time (hours)	LC50 (ppm) Test 1	LC50 (ppm) Test 2
1	1230	>1000
3	1410	>1000
6	940	760
24	211	120
96	75	56

The Toxicity of formalin was not affected by water hardness or pH. However, the toxicity was greater in warm water than in cold water. Mean LC50's in soft water of pH 7.5 at three temperatures were as shown in Table 5.5.

**TABLE 5.5** Mean 50% Lethal Concentrations (LC50's) of Formalin to Striped Bass

Time (hours)	LC50 (ppm) at 12°C	LC50 (ppm) at 17 °C	LC50 (ppm) at 22 °C
1	>1000	>1000	>1000
3	>1000	>1000	750
6	760	455	210
24	120	86	82
96	56	48	30

#### B. Finfish Eggs

FORMALIN-F™ is currently approved for the control of fungi of the family Saprolegniaceae on salmon, trout, and esocid eggs (see 21 CFR 529.1030). Additional safety studies for the control of fungi of the family Saprolegniaceae on other finfish eggs are provided in INAD file 8886. The sponsor, the Upper Midwest Environmental Sciences Center (formerly the U.S. National Biological Service,

Upper Mississippi Science Center), La Crosse, Wisconsin, has authorized the public disclosure of all information within their INAD file 8886.

The data in these studies show that use of the drug at the recommended concentration is safe on the eggs of a wide range of cold and warm water fish. Since, as discussed above, formalin safety has been demonstrated in finfish eggs from a wide variety of species, the safety of formalin would be the same for the eggs of all finfish species. Therefore, these studies are adequate to demonstrate that use of the drug at the recommended concentration is safe on the eggs of all finfish. The following summarizes the finfish egg safety study in INAD 8886.

1. Investigator: Jeffrey J. Rach, M.S.  
National Fisheries Research Center  
National Biological Service  
Department of the Interior  
La Crosse, Wisconsin 54609-0818
2. General Design of the Investigation:
  - a. Purpose of the study: To determine if formalin is safe when administered to finfish eggs of representative finfish species.
  - b. Test Animals: Green eggs of walleye (*Stizostedion vitreum*), channel catfish (*Ictalurus punctatus*), white sucker (*Catostomus commersoni*), common carp (*Cyprinus carpio*), and lake sturgeon (*Acipenser transmontanus*) were tested. The study was conducted at 12±2°C for walleye and white sucker, at 17±2°C for common carp and lake sturgeon and at 22±2°C for channel catfish.
  - c. Dosage form: Formalin solution
  - d. Route of Administration: In the environmental water
  - e. Dosages Used: 1500, 4500, and 7500 ppm formalin
  - f. Test Duration: 45 minute
  - g. Parameters: percent hatch was calculated by the following formula:  
$$\% \text{ hatch} = (\text{number of hatched fry} \div \text{initial number of eggs}) \times 100$$
3. Results:

This study demonstrated that standard formalin treatment, at a concentration of 1000 to 2000 ppm, is safe for finfish eggs of the orders Cypriniformes (common carp and white sucker), Perciformes (walleye) and Siluriformes (channel catfish) for 15 minutes daily, if necessary. Formalin is also safe, at a concentration of 1500 ppm or less, for finfish eggs of the order Acipenseriformes (lake sturgeon) for up to 15 minutes daily. Because the species of finfish eggs treated in the study are

representative of the variety of species of finfish eggs, it is determined that formalin is safe for other finfish eggs. Due to the varying sensitivity of finfish eggs, however, the following statement is included in the labeling.

“A preliminary bioassay should be conducted on a small sub sample of finfish eggs to determine sensitivity before treating an entire group. This is necessary for all species because egg sensitivity can vary with species or strain and the unique conditions at each facility.”

C. Penaeid Shrimp

Target animal safety data from the Freedom of Information (FOI) summary for PMF 3543, 56 FR 20618, May 6, 1991, demonstrated that an adequate margin of animal safety exists when formalin is used as directed by labeling in penaeid shrimp.

## VI. HUMAN SAFETY

Human food safety data for the use of formalin in salmon, trout, catfish, largemouth bass, and shrimp are found in the FOI summary of PMF 3543. The results of four residue depletion studies of formalin in striped bass are summarized below (and found in PMF 5228). The use of formalin has not been shown by these studies to result in the accumulation of formaldehyde above naturally occurring levels in the edible tissue of any of these aquatic species. Because formalin treatment of this wide variety of aquatic species does not result in levels of formaldehyde in the edible tissue above the normal range of endogenous formaldehyde, formaldehyde is not expected to accumulate in additional finfish species, which have not been specifically tested.

Wilmer A. Rogers, Ph.D. at Auburn University, Auburn, Alabama conducted the studies summarized below (and found in detail in PMF 5228). Formalin was administered in the environmental water in all studies and the following method of tissue analysis was used in all studies. Formaldehyde was measured in the muscle of treated and control fish by the Nash test (described in Castell and Smith, *J. Fisheries Research Board of Canada* 30:91, 1973). The Nash test also was used in the residue studies to support the prior approvals for formalin in salmon, trout, catfish, largemouth bass, and shrimp. The recovery of formaldehyde in striped bass muscle samples fortified with 5, 20, and 40 mg/kg formalin was 106.9%, 78.6%, and 70.9%, respectively. The limit of quantitation was 5 mg/kg formalin (1.85 mg formaldehyde/kg fish).

The studies differed from each other as follows:

- A. Juvenile/Indefinite Exposure Period Study - a two-part experiment in which striped bass in tanks were exposed to formalin for an indefinite period of time at two water temperatures.
  - 1. Test Animals: Striped bass; body weight was 23 grams for Part 1 and 39 grams for Part 2.
  - 2. Water Temperatures: 12 to 14°C for Part 1 and 21 to 22°C for Part 2
  - 3. Dose Levels and Treatment Duration: 0 (control) and 25 ppm formalin indefinitely

4. Results: as shown in Table 6.1.

**TABLE 6.1** Mean Formaldehyde Residues (mg/kg) in Muscle of Juvenile Striped Bass

Hours of Exposure to 25 ppm Formalin	Part 1: 12-14 °C		Part 2: 21-22 °C	
	Treated Fish n=2	Control Fish n=2	Treated Fish n=5	Control Fish n=5
0	4.67	3.74	3.26	3.32
12	4.42	4.02	Not collected	not collected
24	4.40	3.85	6.63	5.52
48	4.22	1.67	6.64	3.39
72	5.12	3.84	7.60	5.34
96	4.12	3.63	5.61	4.41
120	2.36	2.71	4.02	4.03
144	1.76	1.76	4.63	4.58
168	3.60	3.74	4.04	3.86

B. Fingerling/Short Duration Bath Study - striped bass in tanks were exposed to formalin for one hour.

1. Test Animals: Striped bass; body weight was 26 grams
2. Water Temperature: 21°C
3. Dose Levels and Treatment Duration: 0 ppm (control) and 250 ppm formalin for 1 hour

4. Results: as shown in Table 6.2.

**TABLE 6.2** Mean Formaldehyde Residues (mg/kg) in Muscle of Fingerling Striped Bass

Hours After Addition of 250 ppm Formalin	Treated Fish n = 4	Control Fish n = 4
0	2.86	3.57
12	3.67	3.17
24	3.73	3.61
48	2.65	2.97
72	3.37	3.38

- C. Market Size/Indefinite Exposure Period Study - market size striped bass in tanks were exposed to formalin indefinitely.

1. Test Animals: Striped bass; body weight was 435 grams
2. Water Temperature: 24°C
3. Dose Levels and Treatment Duration: 0 ppm (control) and 25 ppm formalin indefinitely
4. Results: as shown in Table 6.3.

**TABLE 6.3** Mean Formaldehyde Residues (mg/kg) in Muscle of Market-Size Striped Bass

Hours of Exposure to 25 ppm Formalin	Treated Fish n = 2	Control Fish n = 2
0	3.29	4.00
48	3.98	4.42
96	3.85	3.85

- D. Juvenile/Indefinite Exposure Study - striped bass in ponds were exposed to formalin indefinitely.

1. Test Animals: Striped bass; body weight was 137 grams
2. Water Temperatures: 26 to 30°C
3. Dose Levels and Treatment Duration: 0 ppm (control) and 25 ppm formalin indefinitely

4. Results: as shown in Table 6.4.

**TABLE 6.4** Mean Formaldehyde Residues (mg/kg) in Muscle of Juvenile Striped Bass

Hours of Exposure to 25 ppm Formalin	Treated Fish n = 8	Control Fish n = 8
24	3.60	3.78
48	3.50	3.43
72	3.53	3.50
96	3.43	3.37
120	3.63	3.53

Residue depletion data submitted under PMF 3543, 56 FR 20618, May 6, 1991, support a zero-hour pre-harvest withdrawal time for penaeid shrimp treated with the recommended dose of formalin.

E. Human Food Safety Conclusions: Formaldehyde residues in striped bass muscle did not differ between any of the test groups. Formaldehyde did not accumulate as a result of formalin treatment in juvenile or adult striped bass. Residue accumulation was not affected by dose or duration of exposure. Water temperatures between 12 and 30°C did not appear to affect accumulation of formaldehyde residues in striped bass muscle exposed to formalin.

By the studies in PMF 3543 and PMF 5528, the use of formalin at the recommended concentration has not been shown to result in the accumulation of formaldehyde above naturally occurring levels in the edible tissue of a wide range of cold and warm water fish, including striped bass, the most sensitive species or in shrimp. Therefore, these studies are considered adequate to demonstrate that use of the drug in all finfish, all finfish eggs, and on penaeid shrimp at the recommended concentrations will not result in the accumulation of formaldehyde above naturally occurring levels in their edible tissue.



## VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that FORMALIN-F™, when used as recommended, is effective for the control of external parasites (*Chilodonella* spp., *Costia* spp., *Epistylis* spp., *Ichthyophthirius* spp., *Scyphidia* spp., and *Trichodina* spp.) and monogenetic trematode parasites (*Cleidodiscus* spp., *Dactylogyrus* spp., and *Gyrodactylus* spp.) on all finfish, for the control of external protozoan parasites (*Bodo* spp., *Epistylis* spp., and *Zoothamnium* spp.) on penaeid shrimp, and for the control of fungi of the family Saprolegniaceae on the eggs of all finfish.

Fish are minor animal species as defined under 21 CFR 514.1(d). The data submitted (in PMF 5228 and INAD 8886) meet the requirements of that regulation and FDA's "Guidelines for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor use of Animal Drugs" (April 1986). FDA has considered these data, along with other required data, as support for this supplemental NADA (137-687) which was filed for the expansion of the use of formalin as a parasiticide in all finfish and penaeid shrimp, and as a fungicide on the eggs of all finfish.

Data found within PMF 5228 demonstrate that formaldehyde residues in the muscle of striped bass juveniles and adults did not differ between those treated with formalin and non-treated controls. By the studies in PMF 3543 and PMF 5528, the use of formalin at the recommended concentration has not been shown to result in the accumulation of formaldehyde in the muscle of striped bass, salmon, trout, catfish, largemouth bass, or shrimp. Therefore, additional residue depletion studies for other finfish species are not necessary, because these studies are considered adequate to demonstrate that use of the drug in all finfish at the recommended concentration will not result in the accumulation of formaldehyde.

According to the Center's supplemental approval policy, 21 CFR 514.106(b)(2)(vii), this is a Category II change that did not require a reevaluation of the safety and effectiveness data in the parent application.

This product remains an over-the-counter drug for use by a lay-person. Adequate instructions have been provided for its safe and effective use for the label indications.

The Agency has determined under 21CFR25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

**VIII. APPROVED LABELING**

A facsimile label to be used interchangeably with the 1 gallon, 5 gallon, and 55 gallon containers by stamping the appropriate Net Contents, Lot. No. and Expiration Date is attached along with the package insert.

## FORMALIN-F™

(Formaldehyde Solution)

For Control of External Protozoa and Monogenetic Trematodes on All Finfish, for Control of Fungi on All Finfish Eggs, and for Control of External Protozoan Parasites on Penaeid Shrimp

Formalin has been used since 1909 in the United States in the production of sport, commercial, and experimental fishes (Schnick, 1973). FORMALIN-F™ is used as a therapeutant for the control of external parasites on all finfish, for the control of fungi on finfish eggs, and for control of external protozoan parasites on penaeid shrimp.

### CAUTION

Store FORMALIN-F™ indoors in a well-ventilated area away from direct sunlight, heat, sparks, open flame and at a temperature above 40°F. FORMALIN-F™ subjected to temperatures below 40°F causes the formation of paraformaldehyde, a substance that is toxic to fish. Paraformaldehyde can be recognized as a white precipitate at the bottom or on the walls of the container.

Tolerances to FORMALIN-F™ may vary with strains and species of fish, fish eggs and shrimp. While the indicated concentrations are considered safe for the indicated fishes, a small number of each lot to be treated should be used to check for any unusual sensitivity to formalin before proceeding. A preliminary bioassay should be conducted on a small subsample of finfish eggs to determine sensitivity before treating an entire group. This is necessary for all species because egg sensitivity can vary with species or strain and the unique conditions at each facility.

Under some conditions, fish or penaeid shrimp may be stressed by normal treatment concentrations. Heavily parasitized or diseased fish or penaeid shrimp often have a greatly reduced tolerance to formalin. Such animals do not tolerate the normal tank treatment regimen the first time they are treated, and the time or dosage or both may need to be reduced. If the fish show evidence of distress (by piping at the surface), the solution should be removed and replaced with fresh, well-aerated water. Careful observations should always be made throughout the treatment period whenever tank or raceway treatments are made. Treatments in tanks should never exceed 1 hour for fish or 4 hours for penaeid shrimp (even if they show no signs of distress), nor should it exceed 15 minutes for fish eggs.

Do not apply FORMALIN-F™ to ponds with water warmer than 27°C (80°F), when a heavy bloom of phytoplankton is present, or when the concentration of dissolved oxygen is less than 5 mg/L (5 ppm). FORMALIN-F™ may kill phytoplankton and can cause depletion of dissolved oxygen. If oxygen depletion occurs, add fresh, well-aerated water to dilute the solution and to provide oxygen.

Because formalin may harm a biofilter, biofilters should be by-passed during treatment, and the system flushed and replaced with untreated water before reconnecting the biofilter.

Do not discharge the contents of fish or shrimp treatment tanks into natural streams or ponds without thorough dilution (greater than or equal to 10x). Do not discharge the contents of egg treatment tanks into natural waters without a 100x dilution. This will avoid damage to formalin-sensitive phytoplankton, zooplankton, and fish populations and avoid depletion of dissolved oxygen.

### CHEMISTRY

FORMALIN-F™ is the aqueous solution of formaldehyde gas and contains not less than 37% (by weight) of formaldehyde gas per weight of water and 6 to 13% (12%) methanol. In solution, formaldehyde is present chiefly as HO(CH<sub>2</sub>O)H. Its molecular weight is 30.93. FORMALIN-F™ is readily miscible with water, methanol and ethanol and is slightly soluble in ether. It is a clear, colorless liquid (Heyden Newport Chemical Corporation, 1961).

### FISH AND SHRIMP TOXICITY STUDIES

The toxicity of formalin was measured by standard methods in laboratory bioassays with rainbow trout, Atlantic salmon, lake trout, black bullhead, channel catfish, green sunfish, bluegill, smallmouth bass, largemouth bass, and striped bass. The 3, 6, 24, and 96-hour LC<sub>50</sub> (lethal concentration for 50% of the animals) values for trout range from 1,230 to 100 (microliters per liter=μL/L or ppm); for catfish, from 495 to 65.8 μL/L; for bluegill, from 2,290 to 100 μL/L; and for largemouth bass, the values for 6 to 96 hours range from 1,030 to 143 μL/L (Bills et al., 1977). The 1, 3, 6, 24, and 96-hour LC<sub>50</sub> for striped bass range from 1,230 to 30 μL/L (Bills et al., 1993). The 96-hour LC<sub>50</sub> for striped bass was 60.1 μL/L and no mortality occurred at 250 μL/L for up to 1.5 hours (Wilbur Rogers, Auburn University). The 24, 48, 72, and 96-hour LC<sub>50</sub> values for penaeid shrimp range from 712 to 235 μL/L (ppm)(Johnson, 1974 and Williams, 1980).

## DIRECTIONS FOR USE ON ALL FINFISH

FORMALIN-F™ is effective for the control of external parasites on all finfish. Organisms controlled include the protozoa: *Ichthyophthirius* spp. ("Ich"), *Chilodonella* spp., *Costia* spp., *Epistylis* spp., *Scyphidia* spp., and *Trichodina* spp.; and monogenetic trematodes: *Cleidodiscus* spp., *Gyrodactylus* spp., and *Dactylogyrus* spp.

**Concentrations** – Concentrations used for treatments are expressed as microliters (μL) of FORMALIN-F™ (37% formaldehyde) per liter of water and are equivalent to parts per million (ppm).

**TABLE 1. Concentrations required for control of parasites on the following fish.**

Fish	Concentration of FORMALIN-F™ μL/L	
	Tanks and raceways (for up to 1 hour)	Earthen ponds (Indefinitely)
Salmon and Trout		
above 50°F	up to 170	15-25 <sup>1,2</sup>
below 50°F	up to 250	15-25 <sup>1,2</sup>
All other finfish	up to 250	15-25 <sup>1,2</sup>

<sup>1</sup> Use the lower concentration when ponds, tanks, or raceways are heavily loaded with phytoplankton or finfish to avoid oxygen depletion due to the biological oxygen demand created by decay of dead phytoplankton. Alternately, a higher concentration might be used if dissolved oxygen is strictly monitored.

<sup>2</sup> Although the indicated concentrations are considered safe for cold and warmwater finfish, a small number of each lot or pond to be treated should always be used to check for any unusual sensitivity to formalin before proceeding.

**TABLE 2. Amounts of FORMALIN-F™ needed to supply effective concentrations in selected volumes of water.**

Amount of FORMALIN-F™ needed to give the following concentration of μL/L				
Volume of Water	15	25	170	250
10 gallons	0.60 mL	0.95 mL	6.4 mL	9.5 mL
100 liters	1.50 mL	2.50 mL	17.0 mL	25.0 mL
1 acre foot	4.86 gal	8.10 gal		

## METHODS OF APPLICATION

**Application to tanks and raceways** - Turn off water supply, provide aeration, apply appropriate amount of FORMALIN-F™ and thoroughly dilute and mix to assure equal distribution of FORMALIN-F™. Treat for up to 1 hour, then drain the solution and refill the tank with fresh, well-aerated water. While tank is under treatment, adequate oxygen must be present to maintain the fish. If needed, aeration should be provided to prevent oxygen depletion. Treatments may be repeated daily until parasite control is achieved.

**Application to ponds** - Apply greatly diluted FORMALIN-F™ to the pond evenly using a pump, sprayer, boat bailer, or other suitable device to assure even distribution. Allow FORMALIN-F™ to dissipate naturally. Single treatments usually control most parasites, but may be repeated in 5 to 10 days if needed. Treatments for *Ichthyophthirius* spp. should be made at 2-day intervals until control is achieved.

## DIRECTIONS FOR USE ON ALL FINFISH EGGS:

FORMALIN-F™ is effective for the control of fungi (Saprolegniaceae family) on eggs of all finfish.

**Concentrations** - Apply concentration of 1,000 to 2,000 μL/L (3.8 to 7.6 mL/gallon of water) to eggs of all finfish except Acipenseriformes. The most widely used concentration is about 1,670 μL/L. Eggs of Acipenseriformes should be treated only with concentrations up to 1,500 μL/L.

**Method of application** - Apply as constant flow to water supply of incubating facilities for 15 minutes. Repeat treatment as often as necessary to control growth of fungi. A preliminary bioassay should be conducted on a small subsample of fish eggs to determine sensitivity before treating an entire group. This is necessary because egg sensitivity can vary with species or strain and the unique conditions at each facility.

## DIRECTIONS FOR USE ON PENAEID SHRIMP

FORMALIN-F™ is effective for the control of external protozoan parasites on penaeid shrimp. Organisms controlled include *Bodo* spp., *Epistylis* spp., and *Zoothamnium* spp.

**Concentrations** – Apply concentrations of 50 to 100 µL/L in tanks and raceways for up to 4 hours, and 25 µL/L in earthen ponds for an indefinite period.

**Method of application** - Treat for up to 4 hours daily in tanks or raceways. Treatment may be repeated daily until parasite control is achieved. Use the lower concentration when tanks or raceways are heavily loaded with phytoplankton or shrimp to avoid oxygen depletion due to the biological oxygen demand created by decay of dead phytoplankton. Alternatively, a higher concentration might be used if dissolved oxygen is strictly monitored. Treat earthen ponds for an indefinite period. Treatment may be repeated in earthen ponds in 5 to 10 days, if needed.

## HUMAN WARNING

Exposure to high concentrations of formaldehyde vapor causes severe respiratory irritation, which can be life threatening. Lower vapor levels can cause irritation to the eyes, respiratory tract, and skin. Swallowing formaldehyde can be life threatening. Formaldehyde is an irritant when splashed on skin or into the eye. It can cause severe eye damage, even blindness.

## EMERGENCY FIRST AID

**INHALATION (Breathing):** Vacate exposure area and go to an area of fresh air. (If moving a victim from an area of very high vapor concentrations use a self-contained breathing apparatus.) If the victim is not breathing, give artificial respiration, preferably mouth-to-mouth. Seek medical help immediately.

**INGESTION (Swallowing):** If the person is conscious, dilute, inactivate, or absorb the formaldehyde by giving milk, activated charcoal or water. Get medical help immediately. If vomiting occurs, keep head lower than hips.

**EYE CONTACT:** Immediately flush eye(s) with large amounts of water for at least 15 minutes, lifting the lower and upper eyelids occasionally, until no evidence of chemical remains. Seek medical attention immediately.

**SKIN CONTACT:** Remove contaminated clothing (including shoes) immediately. Wash affected area of body with soap and large amounts of water until no evidence of chemical remains (at least 15 minutes). If there are chemical burns, or appreciable eye or respiratory irritation, get medical help immediately.

## HUMAN PRECAUTIONS

- **Keep out of reach of children**
- **Potential Cancer Hazard:** Formaldehyde vapor has been shown to be carcinogenic in laboratory animals when inhaled. Use applicable safe protection. (Note: This drug, used as labeled, does not cause formaldehyde tissue residues in fish.)
- **Employers:** Refer to Occupational Safety and Health Administration OSHA regulation 29 CFR 1910.1048 for human safety guidance that may be applicable to your specific operation. OSHA's "action level" concentration for airborne formaldehyde is 0.5 part per million (ppm) calculated as an 8 hour time-weighted average (TWA). Use respiratory, skin and eye protection when needed. Refer to OSHA's regulation 29 CFR 1910.1048. OSHA's airborne exposure limits (without use of a respirator) for formaldehyde shall not exceed:
  - 1) 0.75 part per million (ppm) as an 8 hour time weighted average (TWA), or
  - 2) 2.00 parts per million (ppm) as a 15-minute short-term exposure limit (STEL).

**Note:** The odor of formaldehyde in the air can generally be detected at about 0.5 to 0.8 ppm (range about 0.05 to 1 ppm).
- Use only with adequate ventilation.
- Keep container tightly closed when not in use.
- May aggravate a pre-existing asthmatic condition and allergic rhinitis.
- Moderate fire and explosion hazard exists when exposed to heat or flame.
- Contains methanol - cannot be made non-poisonous. Prolonged exposure to methanol has been associated with reproduction disorders.

### ENVIRONMENTAL PRECAUTIONS

- Do not discharge the contents of fish or shrimp treatment into natural streams or ponds without thorough dilution (greater than or equal to 10x). Do not discharge the contents of egg treatment tanks without a 100x dilution. This will avoid damage to Formalin-F™ sensitive phytoplankton, zooplankton, and fish populations and avoid depletion of dissolved oxygen.
- Formaldehyde is identified by the U.S. Environmental Protection Agency (EPA) as a toxic pollutant and hazardous substance and is required by regulation (40 CFR part 122) to be identified as a discharge for NPDES permits for aquatic animal production facilities, aquaculture projects and other facilities.
- Formaldehyde is subjected to SARA Title III, Section 313 reporting. Use, storage, and disposal of this product must be handled in accordance with applicable local, state, and Federal laws.

### HOW SUPPLIED

FORMALIN-F™ is supplied as an aqueous solution in 1 gallon, 5 gallon, and 55 gallon containers.

**Storage:** Store at temperature above 40°F (4.4°C). DO NOT EXPOSE TO DIRECT SUNLIGHT. Recommended storage temperature 50-90°F.

### MANUFACTURED FOR

NATCHEZ ANIMAL SUPPLY CO.  
P.O. Box 1528, 201 John R. Junkin Drive  
Natchez, MS 39120  
(601) 445-0997

**NADA 137-687, Approved by FDA**

Label Rev. 11/02

# Facsimile Container Label

## HUMAN WARNING

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## EMERGENCY FIRST AID

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## HUMAN PRECAUTIONS

- **Keep out of reach of children**
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  - 1) 0.75 part per million (ppm) as an 8 hour time weighted average (TWA), or
  - 2) 2.00 parts per million (ppm) as a 15-minute short-term exposure limit (STEL).Note: The odor of formaldehyde in the air can generally be detected at about 0.5 to 0.8 ppm (range about 0.05 to 1 ppm).
- Use only with adequate ventilation.
- Keep container tightly closed when not in use.
- May aggravate a pre-existing asthmatic condition and allergic rhinitis.
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- Contains methanol - cannot be made non-poisonous. Prolonged exposure to methanol has been associated with reproduction disorders.

## ENVIRONMENTAL PRECAUTIONS

- Do not discharge the contents of fish or shrimp treatment into natural streams or ponds without thorough dilution (greater than or equal to 10x). Do not discharge the contents of egg treatment tanks without a 100x dilution. This will avoid damage to **FORMALIN-F™** sensitive phytoplankton, zooplankton, and fish populations and avoid depletion of dissolved oxygen.
- Formaldehyde is identified by the U.S. Environmental Protection Agency (EPA) as a toxic pollutant and hazardous substance and is required by regulation (40 CFR part 122) to be identified as a discharge for NPDES permits for aquatic animal production facilities, aquaculture projects and other facilities.
- Formaldehyde is subjected to SARA Title III, Section 313 reporting.
- Use, storage, and disposal of this product must be handled in accordance with applicable local, state, and Federal laws.

Storage: Store at temperature above 40°F (4.4°C). DO NOT EXPOSE TO DIRECT SUNLIGHT. Recommended storage temperature 50-90°F.

Lot No:

Exp. Date:

# FORMALIN-F™

PARASITICIDE FOR ALL FINFISH & PENAEID SHRIMP  
AND FUNGICIDE FOR ALL FINFISH EGGS

ACTIVE DRUG INGREDIENT:

Formalin (aqueous solution of formaldehyde)

GUARANTEED ANALYSIS:

Formaldehyde (CH <sub>2</sub> O).....	37%
Water and inert ingredients.....	50-57%
Methanol.....	6-13%

READ ENTIRE PACKAGE INSERT BEFORE USING THIS PRODUCT

KEEP OUT OF THE REACH OF CHILDREN

NET CONTENTS:

MANUFACTURED FOR:

NATCHEZ ANIMAL SUPPLY COMPANY

NATCHEZ, MS 39120

NADA 137-687, Approved by FDA



## FOR ALL FINFISH

**INDICATIONS:** For the control of the following external protozoan parasites: Ichthyophthirius spp. ("Ich"), Chilodonella spp., Costia spp., Epistylis spp., Scyphidia spp., and Trichodina spp., and for the monogenetic trematodes: Cleidodiscus spp., Gyrodactylus spp., and Dactylogyrus spp.

**DIRECTIONS FOR USE:** Apply 170 to 250 microliters per liter ( $\mu\text{L/L}$ ) equivalent to parts per million (ppm) FORMALIN-F™ daily for up to 1 hour in tanks and raceways until parasite control is achieved. Apply single treatment of 15 to 25  $\mu\text{L/L}$  (ppm) FORMALIN-F™ in ponds. May be repeated in 5 to 10 days if needed. For additional details, see package insert.

## FOR ALL FINFISH EGGS

**INDICATIONS:** For the control of fungi of the Saprolegniaceae family

**DIRECTIONS FOR USE:** Apply 1,000 to 2,000  $\mu\text{L/L}$  (ppm) FORMALIN-F™ for 15 minutes to egg treatment tanks to all finfish eggs except Acipenseriformes. For Acipenseriformes, apply up to 1,500  $\mu\text{L/L}$  for 15 minutes. For additional details, see package insert.

## FOR PENAEID SHRIMP

**INDICATIONS:** For control of external protozoan parasites Bodo spp., Epistylis spp., and Zoothamnium spp.

**DIRECTIONS FOR USE:** Apply concentrations of 50 to 100  $\mu\text{L/L}$  in tanks and raceways for up to 4 hours and 25  $\mu\text{L/L}$  in earthen ponds for an indefinite period and repeat in 5 to 10 days if needed. For additional details, see package insert.

## CAUTION

Do not use FORMALIN-F™ that has been subjected to temperatures below 40°F or allowed to freeze. Cold or freezing causes the formation of paraformaldehyde, a substance that is toxic to fish. Paraformaldehyde can be recognized as a white precipitate at the bottom or on the walls of the container.

Tolerances to FORMALIN-F™ may vary with strains and species of fish, fish eggs and shrimp. While the indicated concentrations are considered safe for the indicated fishes, a small number of each lot to be treated should be used to check for any unusual sensitivity to formalin before proceeding. A preliminary bioassay should be conducted on a small subsample of finfish eggs to determine sensitivity before treating an entire group. This is necessary for all species because egg sensitivity can vary with species or strain and the unique conditions at each facility.

Under some conditions, fish or penaeid shrimp may be stressed by normal treatment concentrations. Heavily parasitized or diseased fish or penaeid shrimp often have a greatly reduced tolerance to formalin. Such animals do not tolerate the normal tank treatment regimen the first time they are treated, and the time or dosage or both may need to be reduced. If the fish show evidence of distress (by piping at the surface), the solution should be removed and replaced with fresh, well-aerated water. Careful observations should always be made throughout the treatment period whenever tank or raceway treatments are made. Treatments in tanks should never exceed 1 hour for fish or 4 hours for penaeid shrimp (even if they show no signs of distress), nor should it exceed 15 minutes for fish eggs.

Do not apply FORMALIN-F™ to ponds with water warmer than 27°C (80°F), when a heavy bloom of phytoplankton is present, or when the concentration of dissolved oxygen is less than 5 mg/L (5 ppm). FORMALIN-F™ may kill phytoplankton and can cause depletion of dissolved oxygen. If oxygen depletion occurs, add fresh, well-aerated water to dilute the solution and to provide oxygen.

Because formalin may harm a biofilter, biofilters should be by-passed during treatment, and the system flushed and replaced with untreated water before reconnecting the biofilter.